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THE INTERNAL SECRETION OF THE MAMMAE AS A FACTOR IN THE ONSET OF LABOR.*

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The importance of the internal secretions has come to be well recognized in modern physiology and certain of these secretions, notably that of the thyroid and suprarenals, have been turned to great practical account in modern therapy. The profound influence of one organ or gland upon another organ or gland, through the stimulus of its peculiar internal secretion, has also been brought to light through the masterly researches of Bayliss and Starling.¹ The rapid secretion of the pancreatic fluid under the influence of secretin is a sight that will never be forgotten when witnessed for the first time, and when one recalls the former difficulty of getting even a few cubic centimeters of the pancreatic secretion. It would lead us too far afield from the subject of the present communication even to mention the various hormones which have been discovered since Bayliss and Starling's first epoch-making research upon secretin, not to mention the various applications of the hormone theory to biochemical phenomena that have been made in the past few years.² Among these may be mentioned the fact, however, that Miss Lane-Claypon and Starling³ have shown that the stimulus to the hypertrophy and lacteal activity of the mammary gland in pregnant animals comes not from the ovaries, or placenta, or uterus, but from the fetus itself. These observers found that injections of aqueous extracts of rabbit fetuses into a virgin rabbit every one to three days over a period of three weeks, led the glands, which were at first almost invisible, to become markedly hypertrophied, with enlargement of the ducts and epi-

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¹ The Croonian Lectures, *Lancet*, 1905, 1, 2.

² Armstrong, H. E., and Armstrong, E. F., *Proc. Roy. Soc.*, 1910, S.B., 82, p. 588; *Jour. Lond. Chem. Soc.*, 1910, Abs. II, p. 883.

³ *Proc. Roy. Soc.*, 1905-6, S.B., 77, p. 505. See also for a general discussion of the hormones, Howell, *Science*, 1910, 31, p. 93.

thelium, and to the discharge of a thin fluid and in multiparous rabbits to the discharge of true milk. At present nothing apparently is known concerning the stimulus which brings on the onset of labor in the pregnant female, and nothing as to the cause of premature or delayed labor. It is known of course that this can be accomplished in certain instances by the action of certain drugs, such as ergot; or by mechanical injury to the fetus, or by shock or emotional disturbances or even perhaps by pronounced fatigue, but as yet nothing is known concerning the precise causes which bring about normal labor in the pregnant female.

Our attention was first directed to this subject as the result of our studies on the effect of the colostrum of a cow, ill with parturient paresis, on guinea-pigs. It will be seen from Experiment 11, the details of which are given in our second paper, that a pregnant guinea-pig aborted during the first 12 hours following the intraperitoneal injection of 10 c.c. of fresh, first colostrum cream of a cow ill with parturient paresis. Fetus 5.5 cm. in length.

In another case, Experiment 13 (second paper), a pregnant guinea-pig aborted on the fifth day after receiving intraperitoneally 10 c.c. of the colostrum of the cow, ill with parturient paresis, and which had been kept in the refrigerator for 17 days, and neutralized with sodium hydroxid immediately before the injection. Fetus 8 cm. in length.

The unexpected results of these experiments, in so far as the abortion is concerned, naturally led us to believe that the colostrum of the cow, ill with parturient paresis, contains a substance, or substances, capable of stimulating the mother to premature labor; and to the further thought that perhaps this substance, or substances, is not confined to cows suffering from parturient paresis, but is present also in the colostrum of normal cows or for that matter in that of healthy animals generally. For fear that the absorption had been brought about in Experiments 11 and 13 (second paper) by some imperceptible mechanical injury or by the large volume of liquid injected, we have controlled these experiments, on pregnant guinea-pigs, by the injection of normal salt solution and fresh milk from a healthy dairy herd. In this connection the results of Experiment 15 (second paper) are of particular interest.

It will be observed that a pig in the fifth to seventh week of pregnancy did not abort in five days following an injection, intraperitoneally, of 10 c.c. sterile, normal salt solution (0.85 per cent NaCl). Five days after she had received the injection of the normal salt solution, she received by the intraperitoneal injection, 10 c.c. of fresh milk from a healthy dairy herd. This caused no apparent discomfort and no abortion after four days. She now received, by intraperitoneal injection, 8 c.c. of the first, fresh, whole colostrum of a normal cow (second calf), which had been heated to 38° C. immediately before the injection. Following this last injection this pig aborted in 60 hours, giving premature birth to two fetuses, each 6.5 cm. in length, and 60 hours after this she aborted a second time, giving premature birth to one fetus, 7 cm. in length.

That the normal colostrum of the cow contains a substance capable of causing abortion in pregnant guinea-pigs is also shown by the results of Experiments 19 and 20.

Experiment 19.—A healthy, female guinea-pig five to seven weeks pregnant received by intraperitoneal injection 8 c.c. of skimmed, boiled colostrum from a normal cow. This colostrum was cooled to 38 C. before the injection. The pig showed no discomfort and ate cabbage one hour after the injection. Eight days later she aborted, giving premature birth to two fetuses, one 7 cm. long and weighing 17.7 gms., and the other 7.5 cm. long, and weighing 26.7 gms.

Experiment 20.—A healthy, female guinea-pig, five to seven weeks pregnant, received by intraperitoneal injection 8 c.c. of the whole, fresh normal colostrum. The pig showed no discomfort and ate cabbage one hour after the injection. Had no diarrhea and at the end of eight days aborted two fetuses, one of which was 9.5 cm. long and weighed 47.7 gms., the other was about the same size and age. Both were covered with hair.

We have still another case to show that fresh milk from a healthy dairy herd and certain forms of mechanical injury are incapable of bringing about abortion in pregnant guinea-pigs. That such is the case is seen from Experiment 16 (second paper). In this experiment it is evident that the intraperitoneal injection of 10 c.c. of fresh milk does not produce abortion in pregnant guinea-pigs.

Neither did the rupture of a blood-vessel in the peritoneal cavity, with considerable internal hemorrhage as the result of mechanical injury during the injection.

It is evident from these results that the colostrum of the normal cow, as well as that of the cow suffering from parturient paresis, contains a substance, or substances, capable of bringing about abortion in pregnant guinea-pigs.

Whether this substance causing the abortion is a hormone or a toxin can only be determined by further experiment, which we hope to undertake as soon as the necessary material can be obtained.

It will be seen from Experiment 19, however, that the substance, or substances, in the fresh colostrum of the normal cow which excite the pregnant guinea-pigs to premature labor, withstands heating to boiling for a short time. In this respect it is similar to the hormones and differs from the soluble ferments and many toxins. At any rate, we have evidence here of a new and hitherto unrecognized correlation between the mammary glands and the uterus. According to Lane-Claypon and Starling the fetus through its internal secretions stimulates the hypertrophy and lacteal activity of the mammary gland. It is evident from our experiments that the internal secretions of the mammary gland stimulate the mother to labor and the birth of the offspring.

In this connection it is of interest to note that only the mammalia carry their young, and therefore have labor.

We hope to continue these experiments with the view of learning something as to the precise nature of the substance capable of causing abortion in pregnant guinea-pigs and of determining whether the colostrum of other species of animals, besides the cow, has the power of stimulating the pregnant animal to premature labor.

In conclusion we desire to express our thanks to Mr. J. W. Nutter, assistant in dairying, for much valuable assistance in the practical details of these investigations, and to Professor L. E. Nollau, assistant professor of drawing, for making the photomicrographs used in the illustration of these papers.